

LETTERS AND
CORRESPONDENCE

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Unexplained Bleeding, Arterial Stenosis, Alopecia, and a Splenic Catastrophe

To the Editor: A 33-year-old Hispanic woman presented with an acute abdomen without antecedent trauma or fever. Abdominal exploration revealed massive hemoperitoneum and a lacerated splenic artery, splenic vein, and splenic capsule. Preoperative prothrombin time, partial thromboplastin time, and platelet count were normal. Pathological examination of the spleen revealed two capsular tears in a mildly congested spleen with mild lymphoid hyperplasia. The vessels were grossly unremarkable. A postoperative bleeding time was normal. One week later, during endotracheal intubation for a debridement procedure, the patient developed a pharyngeal hematoma that necessitated emergency tracheostomy. She was seen in hematology clinic for evaluation 2 months after discharge. In retrospect, she had a lifelong history of easy bruisability. Her menstrual flow was normal and two pregnancies and a tonsillectomy had been uncomplicated. Three years previously she had been evaluated for a cold, painful right leg with aorto-femoral angiography (Fig. 1). She was told that she had the “arteries of a ninety-year-old” and bypass surgery was proposed, which she refused. Her mother had died of uterine rupture during childbirth. A brother collapsed and died at the age of 24 while weight-lifting. He was completely bald at the time. His autopsy report showed the cause of death to be transection of the ascending aorta and massive hemothorax.

On examination of this 33-year-old female, no arterial bruits or cardiac murmurs were audible. An ophthalmologic examination revealed astigmatism. Her fingers and toes were long and slender with hyperextensible joints. The wrists and larger joints were unremarkable. No skin hyperextensibility was noted. A venous pattern was visible over the anterior chest wall. Generalized partial alopecia was noted and the outer two-thirds of the eyebrows were missing. The prior tracheostomy and laparotomy incisions had healed with marked hypertrophic scars.

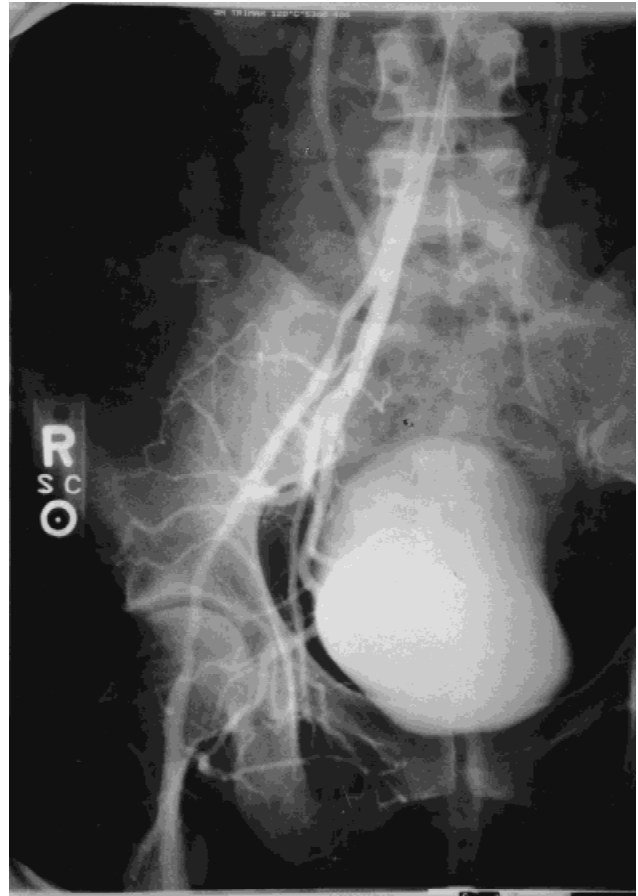


Fig. 1. Aorto-femoral angiography showed a smooth-walled stenotic segment of the right external iliac artery.

A skin biopsy was performed and fibroblast culture generated. Protein gel electrophoretic studies were performed revealing a marked decrease in Type III procollagen. Type I procollagen concentration was normal. A diagnosis of Ehlers-Danlos Syndrome Type IV (ED IV) was made [1]. Review of the angiogram showed smooth-walled narrowing of the right external iliac artery (Fig. 1) that had been interpreted as fibromuscular dysplasia or arteritis. The presence of arterial stenosis in the third decade should raise the suspicion of the arteriopathic form of ED (Type IV). Arterial rupture is the proximate cause of death in the majority of patients; life expectancy in ED IV rarely exceeds the fourth decade [2]. Vascular interventions including arteriography have been associated with fatal complications [3] and are contraindicated. The presence of a hemorrhagic diathesis in the absence of derangement in clotting studies, should lead to the consideration of a disorder in collagen biosynthesis [4]. This report, with a biochemical verification of the diagnosis, provides confirmation of the risk of splenic rupture in ED IV [5], which is rare in contrast to arterial rupture. The absence of more dramatic articular or dermatological findings may make the phenotype more subtle and contribute to a delayed diagnosis. There is no known therapy although Vitamin C is offered in an attempt to improve the concentration of normal Type III procollagen [2].

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A Relapse of Acute Promyelocytic Leukemia After Long-Term Remission of 9.5 Years With Negative PML-RAR α mRNA

To the Editor: The reverse transcription-polymerase chain reaction (RT-PCR) is a useful tool for detecting minimal residual disease (MRD) in some leukemias [1–4]. Relapse of acute promyelocytic leukemia (APL) after long-term remission is rare [4,5]. To our knowledge, this is the first report of APL relapsed after 9.5 years remission even though MRD-negativity was shown in the 6th and 8th years.

A 58-year-old man was admitted to the hospital of Nippon Medical School because of bleeding tendency and anemia in February 1997. He had suffered from APL in 1988 and was treated with combination chemotherapy at our hospital, resulting in complete remission. He then received intensification chemotherapy for 2 years, and the complete remission continued. MRD was checked by RT-PCR analysis for the PML-RAR α transcript of BM cells at 6 and 8 years after diagnosis, and the results were negative. The limit of detection of our RT-PCR assay was one cell per 10^5 to 10^6 cells for PML/RAR α [4]. We performed RT-PCR analysis on relapsed leukemic cells again and detected the PML/RAR α transcript, which was identical to that at onset. He was then treated with *all-trans* retinoic acid (ATRA) therapy (45 mg/m² day) and achieved complete remission again. He is now in complete remission and undergoing chemotherapy.

Although MRD-positivity has been shown to be a potential molecular marker of subsequent clinical relapse in some leukemias [1–4], it is unclear if MRD-positivity is valuable for acute leukemias in long-term remission [4,5]. The present rare case of APL, which relapsed after 9.5 years' remission with negative MRD, is very interesting and important from the point of the biological significance of MRD.

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Intraabdominal Immunoglobulin Light Chain Amyloid Tumor Encompassing a Vascular Malformation

To the Editor: Amyloid is an amorphous substance with structural characteristics that enable it to resist proteolysis and accumulate in tissues. It has been hypothesized that altered vascular permeability may contribute to amyloid deposition [1]. In support of this notion, amyloid deposition within cerebrovascular malformations, although uncommon, has been well documented [2]. However, amyloid deposition in abnormal vessels outside the CNS is distinctly uncommon. We describe an unusual case of a massive amyloid tumor forming around an abdominal arteriovenous malformation (AVM), lending further support to the putative role of vascular anomaly in amyloid deposition.

An 80-year-old man presented with a persistent abdominal mass. Physical examination revealed a large, firm, non-tender RUQ abdominal mass. CT scan showed a 10-cm soft tissue abdominal mass (Fig. 1). Pre-operative evaluation showed a slightly elevated serum protein of 8.2 g/dL (nl 6.0–8.0 g/dL), BUN of 29 mg/dL (nl 7–19 mg/dL), and serum creatinine of 1.3 mg/dL (nl 0.7–1.2 mg/dL). The patient underwent an open incisional biopsy under local anesthesia, whereupon a well-circumscribed, richly vascularized mass was found attached to the omentum. Post-operatively, the serum protein level and 24-hr urine protein quantification were both normal. Because of the patient's advanced age, no further workup or intervention was planned.

The biopsy specimen showed malformed vascular structures encased in masses of amorphous, eosinophilic material (Fig. 1). Aggregates of plasma cells were scattered about. The amorphous material displayed a green birefringence under polarizing light on Congo red stain, characteristic of amyloid protein. Immunohistochemical analysis demonstrated that the amyloid was composed of λ immunoglobulin light chain. Moreover, the plasma cells were monoclonal, expressing monotypic λ light chain. Thus, these findings are consistent with an intraabdominal amyloid tumor arising in a plasma cell dyscrasia and encircling an underlying AVM.

The present case underscores the relationship of amyloid deposition and vascular abnormalities. Previous investigations of the pathogenesis of amyloidosis have implicated the role of preexisting alterations of the microvasculature, allowing excessive leakage of plasma protein. A model using

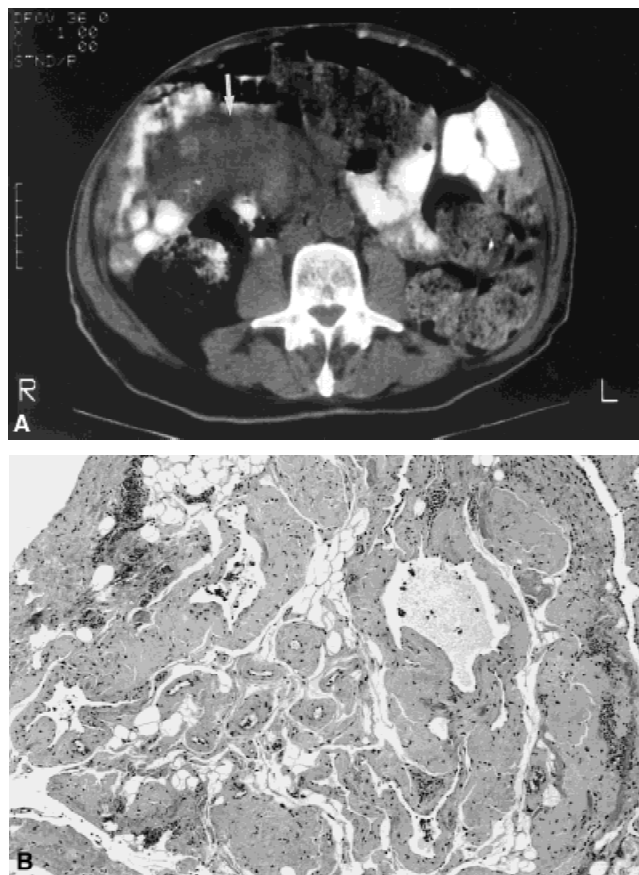


Fig. 1. A: Prominent soft tissue mass (arrow) in the right abdominal cavity as evidenced by CT scanning with oral contrast (original magnification). B: Proliferation of malformed blood vessels of widely varying caliber, ranging from capillaries to tortuous arteriovenous hybrids. Amyloid deposits are found within vessel walls and adjacent to malformed vessels (H&E, $\times 80$).

experimentally induced amyloidosis in mice demonstrated that amyloid proteins preferentially accumulated around leaky vasculature [1].

AVMs are characterized by abnormal shunting of arterial blood directly into the venous system without passing through the capillaries. The resulting marked increase in the plasma flow volume, coupled with vascular wall abnormalities in AVMs, may perhaps predispose the local tissues to amyloid protein accumulation. In support of this notion, several cases of focal CNS amyloidosis occurring in malformed but not normal vessel wall have been reported [2]. These cases involved β -amyloid of the senile plaque type, in contrast to the immunoglobulin light chain amyloid involved in our case, suggesting that this phenomenon is not restricted to any specific amyloid type.

In addition to malformations, anecdotal examples of other types of cerebrovascular abnormalities have been described, including giant cell arteritis [3] and rheumatoid vasculitis [2]. Amyloid deposition occurring in preexisting vascular anomalies outside the CNS is rare. We have found only two such reports. One case involved a gastric AVM [4], and another, colonic angiodysplasia [5].

In summary, this is an unusual case of a massive intraabdominal amyloid tumor arising in the setting of a concurrent plasma cell dyscrasia and AVM. In conjunction with other anecdotes of vascular anomalies containing amyloid, this case supports the notion that amyloid deposition is pathogenetically associated with alterations of the local vasculature.

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Appearance of an Inhibitor to Factor VIII in a Hemophilia A Patient With HIV Infection Treated With Combination Anti-Retroviral Therapy

To the Editor: Many hemophilia A patients with inhibitors who acquired HIV infection have lost their inhibitors as immunodeficiency progressed. We have followed a hemophilia A patient who prior to HIV infection never had an inhibitor. After treatment of HIV infection with combination anti-retroviral therapy including HIV protease inhibitors, the patient's immune function improved and was associated with development of a low-titer antibody to factor VIII.

A 22-year-old male was diagnosed with severe hemophilia A ($<1\%$ factor VIII) at birth. HIV infection was diagnosed in 1986. Annual Bethesda screens for factor VIII antibodies were always negative. In April 1996, he was begun on combination anti-retroviral therapy (indinavir, lamivudine, and stavudine). In October 1997, his CD4 lymphocyte count was $280/\mu\text{l}$, the highest level achieved in this patient, and the HIV viral load was undetectable. In November 1997, he developed soft tissue bleeding involving the left forearm and right calf, which did not respond to routine replacement therapy with 1,000 U recombinant factor VIII. A PTT mixing study with patient and normal plasma did not correct, and a Bethesda assay identified a factor VIII antibody titer of 0.5 U/ml. Therapy was changed to prothrombin complex concentrate with resolution of bleeding symptoms. One month later, a repeat Bethesda titer was 0.7 U/ml.

Improvement or resolution of coagulation inhibitors is one of the sequelae of HIV infection in hemophiliacs. With the advent of HIV protease inhibitor drugs and the use of combination therapy, substantial improvement in immune function is being reported in these patients. The widespread use of successful anti-retroviral therapy in hemophiliacs with HIV infection may result in an increased incidence of inhibitors in these patients.

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